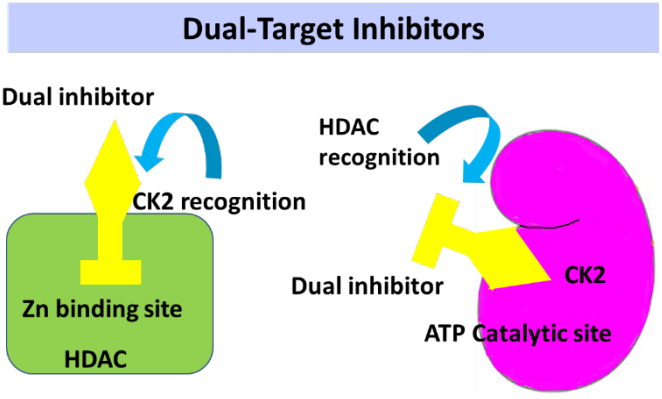
DUALITY: An Integrated Computational and Experimental Approach to Rapid Synthesis of Highly Selective Dual-Targeted HDAC/CK2, MMP2/CK2 Inhibitors

Summary of the project

Cancer is a very complex multi-genetic disease that involves multiple crosstalks between signaling networks. The use of cocktails of several anticancer agents interfering with different mechanisms has been the standard treatment to prevent the problems of resistance. An alternative strategy, which is gaining interest in drug discovery, is the development of a single compound capable of modulating multiple targets simultaneously. They exhibit better therapeutic safety and efficacy, compared with single-target drugs, avoid problems of drug-drug interactions and require less clinical trials than combination therapies.

One of the aims of this project was the design and development of multi-targeted molecules based on the inhibition of two enzymes involved in tumor processes: Histone Deacetylase type 1 (HDAC1) and protein kinase CK2.



The hosted researcher has designed a series of HDAC/CK2 dual inhibitors provided with sub-nanomolar activity against both CK2 and HDAC1, therefore having promising utility as dual-targeting agents for cancer. Remarkably, the best compound showed 3.0 and 3.5 times higher inhibitory activity than the reference single-targeted compounds CX-4945 (CK2 inhibitor in Phase 2 clinical trials) and SAHA (FDA approved HDAC inhibitor), respectively. This potent candidate exhibited micromolar activity in cell-based cytotoxic assays against multiple cell lines. The results of our systematic investigations were submitted for publication in ACS Medicinal Chemistry Letters and the publication is under revision (Special Issue Maurizio Botta).

The researcher devoted his secondment period in Hospital La Fe (Valencia, Spain) under the supervision of Prof. Antonio Pineda to get experience in the main physicochemical techniques to study drug-target interactions, such as NMR techniques (STD and waterLOGSY), Isothermal Titration Calorimetry (ITC), and Surface Plasmon Resonance (SPR). He expressed Matrix metalloproteinase-13 (MMP13), a protein that plays a key role in the degradation of type II collagen in cartilage and bone in osteoarthritis (OA) and studied its interaction with MMP13 inhibitors designed and synthesized in the USPCEU research group.

Inhibiting protein function selectively is a major goal of modern drug discovery. Proteolysis targeting chimeras (PROTACs) represent an emerging technique that is receiving much attention in the development of therapeutics. These bi-functional molecules contain a ligand to bind the target protein, and another ligand to recruit an E3 ligase that will degrade the protein. In this project, the researcher designed and synthesized some PROTAC molecules to bind specifically CK2 and Cereblon E3 ligase, and the evaluation of their biological activity is under way.

This project was developed within the Drug Discovery team at University San Pablo CEU, under the supervision of Prof. Ana Ramos and Prof. Beatriz de Pascual-Teresa. The host group has extensive experience in the discovery of new molecules with anticancer activity, also the hosted researcher has taken advantage to a transfer of knowledge, both in drug design using computational techniques and synthesis strategies.

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CORDIS

Publications

1. *CX-4945 derived dual CK2/HDAC inhibitors with nanomolar inhibitory activity against both enzymes*, L. Rangasamy, I. Ortín, C. Coderch, J.M. Zapico, A. Ramos, B. de Pascual-Teresa, ACS Medicinal Chemistry Letters, Manuscript ID ml-2019-00561z (Submitted, Impact Factor 3.746)

2. *Molecular Imaging Probes based on Matrix Metalloproteinase Inhibitors (MMPIs)*, L. Rangasamy, B. Di Geronimo, I. Ortín, C. Coderch, J.M. Zapico, A. Ramos, B. de Pascual-Teresa, *Molecules* **2019**, *24*(16), 2982. DOI:10.3390/molecules24162982 (IF 3.06).

Dissemination activities

Conference talks

- "*Chemistry in Life Sciences" (LS-EuChemS), on CX4945-based scaffolds for the synthesis of dual inhibitors of Protein Kinase 2 (CK2) and Histone Deacetylases (HDACs)"*. Poster presentation. 6th European Chemical Biology Symposium and meeting of the EuChemS Division. April 3-5, 2019, Madrid, Spain.

- *"Protein kinase (CK2) and histone deacetylase (HDAC) hybrid Inhibitors for cancer therapy".* Poster presentation. 6th Symposium of Medicinal Chemistry Young Researchers. Organized by Spanish Society of Medicinal Chemistry *(SQET: Sociedad Española de Química Terapéutica).* June 21, 2019, Madrid, Spain.

- "*Pharmacophore Hybridization to Discover Novel CK2/HDAC Dual Inhibitors"*. Flash presentation. 19th Meeting "New challenges in drug discovery" organized by SEQT and EFMC (European Federation for Medicinal Chemistry). July 8-11, 2019, Vitoria-Gasteiz, Spain.

- *"Dual CK2/HDAC Inhibitors as a New Strategy for Multi-Targeting Antitumor Drug Discovery"*. Poster presentation. 5th Medicinal Chemistry Symposium Young Researchers, organized by the Spanish Society of Medicinal Chemistry. June 22, 2018, Madrid, Spain.

- *"In silico identification of bifunctional CK2/HDAC inhibitors following a structure-based drug design approach".* Poster presentation. 6th SEQT Summer School, organized by the Spanish Society of Medicinal Chemistry and Janssen. June 19-21, 2018, Toledo, Spain.

- *"Structure-based Drug Design of Dual inhibitors of Protein Kinase 2 (CK2) and Histone Deacetylases (HDACs)".* Poster presentation. 8th Meeting of the Paul Ehrlich EuroPhD Network. July 12-14, 2018, Porto, Portugal.

- *"Computational simulations: a useful tool in the teaching of Chemistry"*. Active Participation. 1st USP-CEU Inter-Faculty Teaching Innovation Congress Organized by University of San Pablo CEU. July 2, 2018, Madrid, Spain.

Public engagement activities

Outreach activities

- "Demonstrate the synthesis of aspirin". Animation of a workshop. 19th Week of Science & Innovation at the USP-CEU. (general public and School Children's). November 4-7, 2019, Madrid, Spain

- "Computational Drug Design Approaches". European Researchers' Night. Organized by University San Pablo CEU (General public and School Children's). September 28, 2018 Madrid, Spain.

- *"Computational simulations: a useful tool in the teaching of Chemistry"*. Animation of a workshop. 18th Week of the Science at USP-CEU. (General public and School Children's). November 5-18, 2018

- "*Marie Skłodowska-Curie Actions"*. European Researcher's Night. Organized by Fundación Para El Conocimiento Madri+d. November 27, 2018, Madrid, Spain.

Communication activities

Newspaper Interviews

- *"San Pablo CEU University welcomes a researcher with the Marie Skłodowska-Curie scholarship, specializing in the fight against cancer"* Press article in a Spanish newpaper. La Razon. 7th June 2018

- *"Loganathan Rangasamy is currently performing research investigation at CEU University"*, Press article in a Spanish newpaper. El Economista. 7th June 2018

- *"Loganathan Rangasamy has chosen CEU San Pablo University to develop his Marie Skłodowska-Curie project funded by the European Commission"*. Press article in a Spanish newspaper. Acta Sanitaria. 7th June 2018

- "*Make the headline with the title of "Young Scientists" inspired me to dedicate my life to science*". Interview for a Spanish foundation gathering scientists surrounding Madrid region. Madri+d. 3rd September 2018

University website News

- *"The School of Pharmacy from San Pablo CEU University participates in the VI Symposium on Medical Chemistry for Young Researchers"*. Press Release. CEU Universities News. 28 June 2019

- *"Longathan Rangasamy wins a scholarship to develop anti-cancer drugs"*. Press release. Universidad San Pablo CEU Media Room. 2nd December 2019

- *"Important representation of the Faculty of Pharmacy in the 5th Young Symposium of the SEQT (Sociedad Española de Química Terapéutica)".* Press release. Universidad San Pablo CEU Media Room. 9th September 2018

- *"Participation of one of the University Marie Sklodowska-Curie researchers in international scientific meetings"*. Press release. Universidad San Pablo CEU Media Room. 26th July 2018

- *"San Pablo CEU University wishes to welcome a researcher with the Marie Skłodowska-Curie scholarship, specializing in the fight against cancer".* Press release. Universidad San Pablo CEU Media Room. 7th June 2018

- "*San Pablo CEU University hosts a new postdoctoral researcher for the development of cancer treatments in the Marie Skłodowska-Curie program".* Press release. Universidad San Pablo CEU Media Room. 28th March 2017

Other activities

Research stays

Dr Rangasamy has successfully completed his secondment research work (2 months, 04.02.2019 29.03.2019) under the guidance of Prof. Antonio Pineda-Lucena, Head, Drug Discovery Unit, Instituto de Investigación Sanitaria La Fe, Hospital Universitario y Politécnico La Fe Valencia, Spain. During this period, he worked on biophysical studies of the ligand/protein interaction using NMR techniques (STD, and waterLOGSY), Isothermal Titration Calorimetry (ITC), and Surface Plasmon Resonance (SPR).

Teaching activities

Dr. Rangasamy has contributed to teaching activities, participating in the bilingual program that USP School of Pharmacy offered in collaboration with the University of Chicago. Within this program, he taught Organic and Pharmaceutical Chemistry practical courses for the Pharmacy Degree Students (Curso académico 2017/2018, Química Orgánica II (2º Farmacia Bilingüe) – 6 days prácticas (4 h per day) and Química Farmacéutica I (3º Farmacia Bilingüe) – 6 days prácticas (4 h per day).

He has also participated in the theoretical teaching within the Inter-University Master Program in Drug Discovery in 2018 and 2019. The students in this program are enrolled in the three participating Universities within the Madrid Area (Universidad Complutense, Universidad de Alcalá and Universidad San Pablo CEU) and have very different backgrounds, which constitutes an important challenge that Loganathan was able to face with a high degree of satisfaction.

Supervision of students

Master Thesis "*Design and Synthesis of Small Molecule Proteolysis Targeting Chimera (PROTAC) for Protein Kinase CK2*" by Drew Grant, King's College London, London, UK, (15.09.2019-15.12.2019).